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L7: Entry 17 of 17 File: USPT Feb 12, 1991

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TITLE: Superactive human insulin analogues

Brief Summary Text (12):
Elimination of the C-terminal pentapeptide sequence of the B-chain of insulin, and amidation of the carboxyl group of the newly-formed C-terminus, Phe B25, results in an analogue, des-pentapeptide(B26-B30)-[Phe.sup.B25 -.alpha.-carboxamide]insulin, which has been shown to display comparable potency with the natural hormone. See Nakagawa et al., J. Biol. Chem., 261:7332-41(1986); Cosmatos et al., Int. J. Pept. Prot. Res., 14:457-71 (1979); Casareto et al., Biol. Chem. Hoppe-Seyler, 368:709-16 (1987). Substitution of Phe B25 with several-other amino acid residues, as well as various modifications of the B26-B30 segment of these substituted insulins, led to analogues varying in potency from almost total inactivity to potency higher than natural insulin. Nakagawa et al., J. Biol. Chem., 261, supra; Casareto et al., supra; Nakagawa et al., J. Biol. Chem., 262:10254-58 (1987). Among these, des-pentapeptide(B26-B30)-[Tyr.sup.B25 -.alpha.-carboxamide]insulin and its His.sup.B25 analogue display potency about 270-300% greater than insulin. Based upon these studies, it has been suggested that the B25 amino acid residue of insulin interacts with the receptor, thereby initiating conformational changes in as yet undefined areas of the insulin molecule which are involved in hormone-receptor binding. The B25-receptor interaction may be modulated in a positive or negative manner by the C-terminal B-chain domain, depending on the nature of the modifications to the B25 residue and the extent to which the B chain C-terminal domain has been altered. Nakagawa et al., J. Biol. Chem., 261, supra; Casareto, supra; Nakagawa et al., J. Biol. Chem., 262, supra.